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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,408	02/21/2002	Lars Abrahmsen	13425-053001	1557

26161 7590 07/12/2005

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EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 07/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,408	ABRAHMSEN ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 7-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 7-13, 15, 17-24* is/are rejected.

7)☒ Claim(s) *14 and 16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on April 18, 2005, amending claims 1, 4, 18, 22 and 24, has been entered.

Claims 1, 4 and 7-24 are pending and are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on April 18, 2005, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 8 is drawn to a polynucleotide encoding a fusion protein comprising a functionally equivalent variant of a glutathione S-transferase (GST). Therefore, these

claims are drawn to a genus of polynucleotides encoding polypeptides having any structure. The specification only teaches one species, the polynucleotide encoding a fusion protein having GST. One species is not enough to describe the whole genus and there is no evidence on the record of the relationship between the structure of the polynucleotide encoding GST and the structure of a polynucleotide encoding a variant of GST. The specification also does not describe which residues of a GST are needed to impart the variant with GST activity. Therefore, the specification fails to describe a representative species of the genus of polynucleotides encoding a variant of GST having GST activity.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claim 8.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that establishing a correlation between structure and function satisfies the requirement of the written description. Examiner respectfully disagrees. Even though applicants argue that the specification details that functionally equivalent variants retain the ability to form dimers and have binding properties allowing for affinity purification

and disclose exemplary functionally equivalent variants of GST, the claim is drawn to a wide genus comprising polynucleotides encoding any variants of GST, including any or all variants, mutants and recombinants of any GST, and polypeptides having the ability to form dimers and have binding properties allowing for affinity purification. Therefore, there is not established correlation between structure and function of the claimed genus.

As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.** Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only a few species within the genus. In the instant case the claimed genera of claim 8 includes species which are widely variant in structure. The

genus of claim 8 is structurally diverse as it encompasses polynucleotides encoding GST proteins and any or all mutants, variants or recombinants of any GST having ability to form dimmers and have binding properties allowing for affinity purification. As such, the description of solely functional features present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus. Hence the rejection is maintained.

Claim 8 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide encoding a fusion protein comprising a GST, does not reasonably provide enablement for a polynucleotide encoding a fusion protein comprising of variants of a GST. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claim 8 is drawn to a polynucleotide encoding a fusion protein comprising a functionally equivalent variant of a glutathione S-transferase (GST). Therefore, claim 8

encompasses polynucleotides encoding a fusion protein comprising any variants of a GST. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides encoding GST variants, broadly encompassed by the claims. Since the amino acid sequence of the encoded protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a polynucleotide encoding a fusion protein comprising of a GST. It would require undue experimentation of the skilled artisan to make and use the claimed variants. The specification is limited to teaching the use of a polynucleotide encoding a GST but provides no guidance with regard to the making of variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by this claim.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple

modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of polynucleotides encoding any GST, including variants and mutants, because the specification does not establish: (A) regions of the protein structure which may be modified without affecting GST activity; (B) the general tolerance of GST to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides encoding GST variants and mutants. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of GST variants having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily,

and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that applicants have provided ample guidance for making and using variants of GST that retain the functional property of enabling dimerization of soluble form of human SSAO, including exemplary functionally equivalent variants of GST, and that the skilled artisan would have been able make functionally equivalent variants of a given protein without undue experimentation. Examiner respectfully disagrees. Even though the structure of some variants of GST retaining their functional property of enabling dimerization of soluble form of human SSAO, the claims are not only drawn to variants of GST having specific mutations at residues, but to any or all mutants, variants and recombinants of any GST retaining their functional property of enabling dimerization of soluble form of human SSAO. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation. While the art may teach in general the structure of GST, conserved amino acid sequences, and etc, such

teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art. Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 7, 8-10, 15, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al.

Claims 1, 7-10 are drawn to a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2 or an enzymatically active fragment thereof, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences. Claim 15 is drawn to a vector comprising a polynucleotide encoding said fusion protein and claims 17-19 and 22-24 are drawn to methods of purifying the fusion protein and SSAO.

Smith et al. (form PTO-1449 – reference AYY) teach an amino oxidase that is 100% identical to the semicarbazide-sensitive amino oxidase (SSAO) of SEQ ID NO:2 of the instant invention (Figure 1, page 20 and SwissProt sequence alignment). Smith et al. teach that the transmembrane domain is between residues 5-27 (Figure 1, page 20 and page 21). Art and the specification teach that the soluble from of SSAO lacks the membrane spanning portion of the wild-type SSAO. Even though Smith et al. teaches the transmembrane domain as including residues 5-27 of SEQ ID NO:27, one of ordinary skill in the art would have also recognized the advantage of using amino acids 29 to 763 of SEQ ID NO:2. The amino acid at position 28 is an Arg. There are numerous proteases in the cell and growth medium that cleaves at arginine residues (Huston et al. – U.S. Patent 5,013,653, Column 10, Table 1). To ensure that the fusion partner and SSAO are not cleaved prematurely, it would have been obvious to fuse the protease cleavage site to a SSAO consisting of amino acids 29-763 of SEQ ID NO:2.

The difference between the reference of Smith et al. and the instant invention is that the reference of Smith et al. does not teach a polynucleotide encoding a secreted

fusion protein comprising a signal peptide, a fusion partner, a protease cleavage site and at least one spacer amino acid sequence nor a vector comprising said polynucleotide nor a method of purifying said fusion protein and SSAO.

Huston et al. (U.S. Patent No. 5,013,653 – cited on previous form PTO-892) teach polynucleotide encoding a fusion protein comprising a signal peptide, a target protein and a protease cleavage site between the fusion partner and to the target protein (Column 1). Huston et al. teach that a signal peptide can be used for secretion of the fusion protein and in order protect the target protein from intracellular degradation during expression or isolation/purification(Column 1). Huston et al. also teach that a protease cleavage site can be incorporated between the target protein and any additional fused material (column 1 and 2). Huston et al. also teach a vector comprising said polynucleotide, a method of producing the target protein and a method of immobilizing the fused target protein (Column 2 and Examples 1-4).

Tudyka et al. (form PTO-1449 – Reference ACCC) teach that GST can be used as a fusion partner that enables dimerization of a target recombinant protein and confer enzymatic reporter activity (abstract and page 2180). Tudyka et al. teach that glutathione S-transferase (GST) from *Schistosoma* that is 100% identical to the GST of SEQ ID NO:4 of the instant invention. Tudyka et al. teach that replacing three of the four exposed cysteine residues in GST (residues 85, 138 and 178) prevents misfolding due to incorrect disulfide bonds (abstract, Figure 2-B, page 2182 and 2185) and the resulting GST mutant is 100% identical to SEQ ID NO:5 of the instant invention. Tudyka et al. also teach that the fusion protein was purified by means of an affinity

column with glutathione (abstract) and the GST protein can be proteolytically removed after the fusion protein is produced in the cytoplasm (page 2185).

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising a signal peptide, a fusion partner of Tudyka et al., a soluble form of SSAO of Smith et al., and a protease cleavage site between the fusion partner and to the target protein, as outlined by Huston et al., and also making a polynucleotide encoding a fusion protein comprising a protease, which cleaves at the cleavage site, and a fusion partner. The motivation of making the fusion constructs is to facilitate the secretion, isolation and purification of a soluble SSAO and the protease. The motivation of truncating the transmembrane domain of SSAO is to produce soluble SSAO, thereby increasing the efficiency of the purification process. The motivation of using amino acids 29-763 of SEQ ID NO:2 is to lower the risk of the target protein from being cleaved prematurely by proteases in the cell or cell culture. The motivation of using the fusion partner of Tudyka et al. is to enable dimerization of SSAO and confer enzymatic reporter activity. The motivation of using the mutant GST of Tudyka et al. is to prevent misfolding of the protein. One of ordinary skill in the art would have had a reasonable expectation of success of making a polynucleotide encoding a fusion protein since the individual proteins incorporated into the fusion proteins are well known in the art and Huston et al. and Tudyka et al. in combination teach detailed steps in making a successful fusion protein and methods of purifying the fusion protein and ultimately the protein of interest.

Therefore, the above references render claims 1, 7, 8-10, 15, 17-19 and 22-24 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the cited references did not provide the skilled artisan with the requisite reasonable expectation that the claimed nucleic acid (SSAO) could have been successfully produced, because a soluble form of the protein (SSAO) can not be obtained with a reasonable expectation of success and without undue experimentation. Examiner respectfully disagrees. Smith et al. teaches that the soluble from of SSAO lacks the membrane spanning portion of the wild-type SSAO.

Applicants also argue that it was not known which fusion partner to use, where to fuse it, which signal peptide could be used for secretion of SSAO, which linked could be used between the signal peptide and GST. Examiner respectfully disagrees. In combining the cited references, one having ordinary skill in the art would have been motivated to make the fusion constructs to facilitate the secretion, isolation and purification of a soluble SSAO and use the fusion partner of Tudyka et al. to enable dimerization of SSAO, confer enzymatic reporter activity, or prevent misfolding of the protein. One having ordinary skill in the art would have known to fuse the fusion partner to the N-teriminus or the C-terminus of the protein of interest and use the signal peptide of Hutson et al., since Hutson et al. teaches signal peptides which secrets a fusion protein of interest. Examiner notes that claims 1, 7, 8-10, 15, 17-19 and 22-24 are drawn to any signal peptides.

Applicants argue that the claimed invention permits the production of pure, soluble and active human SSAO and the cited references constitute at best an invitation to vary parameters or try each of numerous possible choices until one possibly arrives at a successful result and lacks a reasonable expectation of success. Examiner respectfully disagrees. As discussed above, one of ordinary skill in the art would have had a reasonable expectation of success of making a polynucleotide encoding a fusion protein since the individual proteins incorporated into the fusion proteins are well known in the art and Huston et al. and Tudyka et al. in combination teach detailed steps in making a successful fusion protein and methods of purifying the fusion protein and ultimately the protein of interest.

Applicants also argue there is a lack of reasonable expectation of success in combining the references because at the time of invention, expression and purification of copper-containing amine oxidases had proven difficult to achieve and that no such protein had been successfully expressed and purified prior to the present application. Examiner respectfully disagrees. Smith et al. teaches expression and purification of a copper-containing amine oxidase, at least one year prior to the filing of the instant application. Therefore, coupled with the teachings of Smith et al. and the cited references, one having ordinary skill in the art would have had a reasonable expectation of success in expressing and purifying SSAO or soluble SSAO.

Applicants also argue that the SSAO was purified in high yield of pure, soluble and highly active recombinant human SSAO. While this may be true, the claims do not recite this limitation.

Hence the rejection is maintained.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al. and Zambidis et al.

Claim 11 is drawn to a polynucleotide encoding a fusion protein consisting of a mouse IgG1 heavy chain signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner, a protease cleavage site and one or more spacer amino acid sequences.

Smith et al., Huston et al. and Tudyka et al., in combination teach a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences and a method of purifying the fusion protein, as discussed above.

The difference between the references of Smith et al., Huston et al. and Tudyka et al. is that the combined references do not teach a polynucleotide encoding a fusion protein having a mouse IgG1 heavy chain signal peptide. Huston et al. only teaches using a human IgG1 as a signal peptide in the fusion protein.

Zambidis et al. (cited on previous form PTO-892) teach a mouse IgG1 heavy chain, used as a signal peptide in a fusion protein (abstract).

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising a mouse IgG1 signal peptide. The motivation of making such a fusion construct is to facilitate the expression, secretion and purification of the target protein. One of ordinary skill in the art would have had a reasonable expectation of success since IgG1 or other immunoglobulin proteins are well known and well practiced in the art in facilitating expression and secretion of heterologous proteins.

Therefore, the above references render claim 11 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the cited references do not provide the skilled artisan with the requisite suggestion, motivation or reasonable expectation of success to combine the references and/or modify the references' teachings to result in the nucleic aid of claim 1. Examiner respectfully disagrees. As discussed above, the cited references do provide the skilled artisan with the requisite suggestion, motivation or reasonable expectation of success to combine the references and/or modify the references' teachings to result in the nucleic aid of claim 1.

Applicants also argue that Zambidis' description of a signal peptide would not have provided a suggestion, motivation or reasonable expectation of success to a skilled artisan to exclude the soluble SSAO the amino acid at position 28 and use amino acids 29-763 of SEQ ID NO:2 or a fragment thereof. Examiner respectfully disagrees.

Zambidis' is relied upon for its teaching of the signal peptide. Smith et al. is relied upon for using a soluble SSAO consisting of residues 29-763 of SEQ ID NO:2. As discussed above, even though Smith et al. teaches the transmembrane domain as including residues 5-27 of SEQ ID NO:27, one of ordinary skill in the art would have also recognized the advantage of using amino acids 29 to 763 of SEQ ID NO:2. The amino acid at position 28 is an Arg. There are numerous proteases in the cell and growth medium that cleaves at arginine residues (Huston et al. – U.S. Patent 5,013,653, Column 10, Table 1). To ensure that the fusion partner and SSAO are not cleaved prematurely, it would have been obvious to fuse the protease cleavage site to a SSAO consisting of amino acids 29-763 of SEQ ID NO:2.

Hence the rejection is maintained.

Claims 12-13 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al., Huston et al. and Tudyka et al. and Brenda Enzyme Database.

Claims 12-13 and 20-21 are drawn to a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner, a protease cleavage site comprising the amino acid sequence of SEQ ID NO:6 and one or more spacer amino acid sequences and a method of purifying the fusion protein.

Smith et al., Huston et al. and Tudyka et al., in combination teach a polynucleotide encoding a fusion protein consisting of a signal peptide, a semicarbazide-sensitive amine oxidase (SSAO) consisting of amino acids 29-763 of SEQ ID NO:2, a fusion partner comprising the amino acid sequence of SEQ ID NO:4 or SEQ ID NO:5, a protease cleavage site and one or more spacer amino acid sequences and a method of purifying the fusion protein, as discussed above.

The difference between the references of Smith et al., Huston et al. and Tudyka et al. is that the combined references do not teach a polynucleotide encoding a fusion protein having a protease cleavage site comprising the amino acid sequence of SEQ ID NO:6.

Huston et al. teaches that many different protease cleavage sites can be introduced into the fusion protein (Columns 9-11). Brenda Enzyme Database (EC 3.4.22.28 – form PTO-892) teach a 3C protease from Coxsackievirus that is 100% identical to SEQ ID NO:6 of the instant invention. The Database also teaches a picornvirus 3C protease and a rhinovirus 3C protease (pages 3-4). There are many types of protease cleavage sites and 3C proteases is one of the many enzymes capable of safely cleaving a fusion partner from the target protein.

Therefore, combining the teaches of the above references, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make a polynucleotide encoding a fusion protein comprising any of the 3C proteases listed in the Brenda Enzyme Database. The motivation of incorporating a cleavage site between the SSAO and GST is to cleave off the GST protein after the

fusion protein is produced in the cytoplasm. One of ordinary skill in the art would have had a reasonable expectation of success since 3C proteases are well known and have been widely used in cleavage sites between target proteins and additional fused material.

Therefore, the above references render claims 12-13 and 20-21 *prima facie* obvious to one of ordinary skill in the art.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the cited references do not provide the skilled artisan with the requisite suggestion, motivation or reasonable expectation of success to combine the references and/or modify the references' teachings to result in the nucleic aid of claim 1. Examiner respectfully disagrees. As discussed above, the cited references do provide the skilled artisan with the requisite suggestion, motivation or reasonable expectation of success to combine the references and/or modify the references' teachings to result in the nucleic aid of claim 1.

Applicants also argue that Brenda's description of a 3C protease amino acid sequences odes not overcome the references' lack of suggestion to construct a secreted SSAO fusion protein wherein the SSAO portion lacks amino acid position 28 and consists of amino acids 29-763 of SEQ ID NO:2 or a fragment thereof. Examiner respectfully disagrees. Brenda is relied upon for its teaching of the signal peptide. Smith et al. is relied upon for using a soluble SSAO consisting of residues 29-763 of SEQ ID NO:2. As discussed above, even though Smith et al. teaches the transmembrane domain as including residues 5-27 of SEQ ID NO:27, one of ordinary

skill in the art would have also recognized the advantage of using amino acids 29 to 763 of SEQ ID NO:2. The amino acid at position 28 is an Arg. There are numerous proteases in the cell and growth medium that cleaves at arginine residues (Huston et al. – U.S. Patent 5,013,653, Column 10, Table 1). To ensure that the fusion partner and SSAO are not cleaved prematurely, it would have been obvious to fuse the protease cleavage site to a SSAO consisting of amino acids 29-763 of SEQ ID NO:2.

Hence the rejection is maintained.

Allowable Subject Matter

Claims 14 and 16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

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